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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 30

Application Number: 08/811,361
Filing Date: March 04, 1997
Appellant(s): MOLLY KULESZ-MARTIN

Michael Dunn
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 5/7/2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows: The rejection of claim 11 as lacking an enabling disclosure based on the lack of utility under 35 USC 101.

(7) Grouping of Claims

There is only one claim.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

No prior art is relied upon by the examiner in the rejection of the claims under appeal.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim 11 is rejected under 35 U.S.C. 101. This rejection is set forth below.

Claim 11 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

The disclosed utilities for the purified p53as peptide is to study cell growth and maturation , detecting normal versus abnormal cell growth and to normalize cell growth of abnormally growing cells (see page 10 line 14-16). However, neither the specification nor any art of record teaches what the purified p53as peptide is, how it functions, or a specific and well-established utility for any of the fragments claimed. Furthermore, the specification does not teach a relationship to any specific disease or establish any involvement in the etiology of any specific disease. The asserted utility of the purified p53as protein is based on the assertion that p53as peptide (SEQ ID NO:6 and7) is structurally similar to mouse and human p53.

The specification further proposes, based on sequence similarity to p53, that the p53 as peptide will have similar biological effects and activities (page 10, line 14-16). However, evidence based on protein sequence homology does not alone permit extrapolation to an isolated amino acid's biological function or use thereof. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of

message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Further, Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of the p53 gene family sulfate transport proteins that included a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter, and 45% similarity to the human sulfate transporter 'downregulated in adenoma'. However, upon

analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al. suggest that these results underscore the importance of confirming the function of newly identified gene products even when the database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph). These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. It cannot be predicted, based on the information in the specification, what affect this difference has on the function of the protein. Further even if the polypeptide of SEQ ID NO:6 and 7 are structurally similar to p53, neither the specification nor any art of record teaches what the polypeptide is, what it does, nor teach a relationship to any specific disease or establish any involvement of the polypeptide in the etiology of any specific disease or teach which fragments might be active as claimed in a pharmaceutical composition.

In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p.

398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Clearly, given not only the teachings of Bowie et al, Scott et al and Burgess et al but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, any dissimilarity, to murine or human p53, the function of the SEQ ID NO:6 and 7 polypeptide could not be predicted, based on sequence similarity with p53, nor would it be expected to be the same as that of murine or human p53.

The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed polypeptide and fragments thereof. Because the claimed invention is not supported by a specific asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

Claim 11 also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

(11) Response to Argument

At page 3 of the Brief, Appellant argues that the specification provided sufficient guidance in terms of distinguishing p53as from p53, and that the specific utility designated for the p53as protein is for the production of an antibody that will react with the p53as protein but will not react with the p53 protein. Based on this assertion, appellant argues that the use of the p53as antibody can help in the detection of the presence of p53 versus p53as and that such distinction will aid in the determination of the two species. This argument is not considered persuasive because the use of a protein for the production of an antibody is not considered a specific and or substantial use of a protein. Any protein or epitope once known can be utilized as an antigen for the production of an antibody. The utilization of the protein as an antigen for the production of an antibody only provides the skilled artisan with a starting point from which make an antibody but does not provide sufficient utility for the protein itself.

At page 4 of the Brief, Appellant argues that the p53as protein and the p53 protein have significant homology except for the carboxy terminal region, wherein there exists a difference. From this, Appellant substantiates their argument by stating that in the absence of the carboxy terminal region or negative regulatory domain, p53as can be utilized as a cancer detection maker. Appellant's arguments have been carefully considered but are not found persuasive because it is appellant's intent to correlate the function of a well known protein, p53, with that of a highly homologous protein, p53as. However, based on the decision made by the Courts of Patent Appeals and Interferences (paper no.17), it was clearly established in the record that because p53as does not show complete homology with that of full length p53, the utilities established for that of p53 cannot be translated or carried over to that of p53as.

At page 5 pf the Brief, Appellant argues that EP 0 709 397 A1 supports the described utilities of the p53as protein. Appellant's arguments have been considered but are not found persuasive because the EP document furnished was appellant's own work and at the time of filing of the instant application, the utilities established for the p53as protein were still not known.For the above reasons, it is believed that the rejections should be sustained.

Therefore, for the reasons set forth above, Appellant's arguments have been fully considered, but are not considered sufficnet to rebut the *prima facie* case of lack of utility and it is believed that the rejections should be sustained.

Respectfully submitted,

CHY
October 30, 2003

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